Guest Editorial

OVERVIEW OF FUNGAL RHINOSINUSITIS

Arunaloke Chakrabarti[1], Ashim Das[2], Naresh K Panda[3]

ABSTRACT : *The incidence of fungal rhinosinusitis has increased to such extent in recent years that fungal infection should be considered in all patients with chronic rhinosinusitis. In India though the disease was reported earlier only from northern regions of this country, nowadays the disease is increasingly diagnosed from other parts as well. The disease has been categorized with possible five types: acute necrotizing (fulminant), chronic invasive, chronic granulomatous invasive, fungal ball (sinus mycetoma), allergic. The first three types are tissue-invasive and the last two are non-invasive fungal rhinosinusitis. However, the categorization is still controversial and open to discussion. Chronic fungal rhinosinusitis can occur in otherwise healthy host and Aspergillus flavus is the common etiological agent in Indian scenario. The pathophysiologic mechanism of the disease remains unclear. It may represent an allergic IgE response, a cell-mediated reaction, or a combination of two. Early diagnosis may prevent multiple surgical procedures and lead to effective treatment. Histopathology and radio-imaging techniques help to distinguish different types and delineate extension of disease process. Culture helps to identify the responsible etiological agent. The presence or absence of precipitating antibody correlates well with disease progression or recovery. The most immediate need regarding management is to establish the respective roles of surgery and antifungal therapy. Non-invasive disease requires surgical debridement and sinus ventilation only, though additional oral or local corticosteroid therapy may be beneficial in allergic type. For invasive disease, the adjuvant medical therapy is recommended to prevent recurrence and further extension. Itraconazole has been found as an effective drug in such situation. Patients with acute necrotizing type require radical surgery and amphotericin B therapy.*

INTRODUCTION

Sinusitis or more accurately rhinosinusitis is a common disorder, affecting approximately 20% of the population at some time of their lives. Whether fungi can exist in sinus mucous without causing disease is unclear. However, fungal rhinosinusitis once considered a rare disorder, is being recognized and reported with increasing frequency over the last two decades worldwide.[1,2] Fungal rhinosinusitis occurs in two distinct forms – the fulminant invasive disease which is predominantly seen in patients with some form of immunosuppression and chronic fungal rhinosinusitis in apparently healthy hosts.[3] The fulminant variety, similar to rhino-cerebral zygomycosis, is well known to clinicians due to its dramatic presentation and poor prognosis. But the existing knowledge regarding chronic fungal rhinosinusitis is quite controversial and often confusing. Chronic fungal rhinosinusitis occurring in otherwise healthy hosts is being recognized with increasing frequency probably due to increased awareness. In India, the disease once considered prevalent only in north India,[4-7] is now reported from other parts of the country as well.[8-10] Thus, it demands attention of clinicians of this country for suspecting and diagnosing those cases.

Though species of Aspergillus is isolated from majority of such cases, dematiaceous hyphomycetes, Pseudallescheria boydii, Candida spp., Fusarium spp., hyalohyphomycetes and Zygomycetes are also reported from some cases.[5,11] Rhinosporidium seeberi produces chronic granulomatous diseases of mucocutaneous tissue of nose and Conidiobolus coronatus produces chronic rhino-facial zygomycosis. These are well-recognized clinical entities and have not been elaborated further in this brief review of fungal rhinosinusitis. Clinicians should keep these entities in mind for differential diagnosis of fungal rhinosinusitis.

HISTORY

Plaignaud possibly reported the first case of fungal sinusitis in 1791; a 22 year old solider with maxillary pain had a "fungal tumor" which was said to be cured by cautery.[12] A more specific diagnosis of nasal and paranasal sinus aspergillosis was reported by Schubert in 1885.[13] This was non-invasive aspergillosis of paranasal sinus. The first well documented case of invasive aspergillosis was reported by Oppe in 1897 in which Aspergillus infection of sphenoid sinus had extended to cerebrum through erosion of bony wall.[14] Finally, recognition of two different forms of paranasal sinus mycoses, one non-invasive behaving clinically like chronic bacterial sinusitis and other invasive, in which the infection results in a mass that behaves like a malignant neoplasm, eroding bone and spreading into adjacent tissue, was established by Hora in 1965.[15] In 1980, McGill et al. reported in immunocompromised patients a third manifestation of fungal rhinosinusitis – a fulminant form with a rapid, malignant course advancing relentlessly to destruction of nasal cavity, sinus and adjacent structures

[1] Department of Medical Microbiology, [2]Histopathology, [3]Otolaryngology, Postgraduate Institute of Medical Education and Research, Chandigarh

such as orbit and brain within a few days. In 1981 Miller et al. recognized a histologic resemblance between the specimens of five patients with allergic broncho-pulmonary aspergillosis (ABPA).[17] Two years later, Katzenstein et al. independently, observed the patho-physiologic resemblance between ABPA and seven cases of chronic fungal sinusitis, leading to a description of fourth type – allergic Aspergillus sinusitis.[18] Later, it became apparent that dematiaceous fungi are also important etiological agents besides Aspergillus species and consequently, the name is changed to allergic fungal sinusitis (AFS).[19]

CATEGORIZATION OF FUNGAL RHINO SINUSITIS

Based on histopathologic findings, five basic diagnostic categories of fungal rhinosinusitis disorders are currently recognized.[20] Clinical presentations are also usually characteristic of each type. The lesion can be broadly divided into two categories the invasive and non-invasive. Three types of fungal rhinosinusitis are tissue–invasive infectious diseases: acute necrotizing (fulminant) fungal rhinosinusitis, chronic invasive fungal rhinosinusitis, and granulomatous invasive (indolent) fungal rhinosinusitis. The two non-invasive fungal rhinosinusitis disorders are fungal ball (sinus mycetoma) and AFS. (Table 1)

Table 1: Features of Fungal Rhinosinusitis

	Host characteristics	Clinical presentation	Histopathology	Treatment	Prognosis
Acute narcotizing (fulminant)	Immunocompromised due to uncontrolled diabetes (commonest) malignancy, cytotoxic therapy	Paranasal anaesthesia or fever, cough, nasal eschar, spreading through soft tissue & bone epistaxis, headache	Widespread necrosis, neutrophilic inflammation, fungal hyphae invading mucosal, blood vessels or bone	Radical debridement & antifungal agent	Poor unless managed early
Chronic invasive	Immunocompromised (commonly due to diabetes mellitus)	Orbital apex syndrome	Fungal invasion into the mucosal & a chronic inflammatory infiltrate, occasionally necrotizing granuloma	Radical debridement & antifungal agent	Good if treated early
Chronic granulomatous invasive	Immunocompetent	Unilateral proptosis, headache	Granuloma with giant cell, palisading histiocytes, scanty, mucosa-invasive fungi in giant cell	Debridement, aeration & Itraconazole	Good, but may recur
Fungal ball (sinus mycetoma)	Immunocompetent, sometimes atopic or previous sinus surgery	Rhinosinusitis often unilateral, nasal obstruction, nasal discharge, nasal polyp, calcification on CT	Dense accumulation of fungal elements in mucoid matrix, low grade chronic inflammation in adjacent mucosa	Debridement, aeration	Excellent
Allergic	Immunocompetent, frequently atopic	Pansinusitis, nasal polyps, proptosis, calcification on CT	Sparse fungal elements in eosinophil-rich mucoid material (allergic mucin) lymphoplasmocytic & eosinophilic response in adjacent mucosa	Debridement, aeration, oral & topical corticosteroid, Immunotherapy	Recurrence common

INVASIVE FUNGAL RHINOSINUSITIS DISORDER

Acute necrotizing (fulminant) fungal rhinosinusitis: Although most common in patients with uncontrolled diabetes mellitus and other immunosuppressed patients, it occasionally occurs in previously healthy persons.[21] It often starts as painless necrotic black palatal or nasal septal ulcer or eschar, spreading through mucosa into juxtaposed soft tissues and bone. Saprophytic fungi of the order Mucorales, including species under Rhizopus, Rhizomucor, Absidia, Mucor, Cunninghamella, Saksenaea, Apophysomyces, are usual etiological agents. Occasionally species of Aspergillus, Fusarium & Pseudallescheria boydii may cause chronic invasive fungal rhinosinusitis in immunocompetent host.[24]

Clinically the patient with acute necrotizing (fulminant) fungal rhinosinusitis presents with fever, cough, crusting of nasal mucosal, epistaxis, and headache. The lesion starts as a nasal eschar, spreading through mucosa into juxtaposed soft tissues and bone. Histopathological studies show hyphal invasion of blood vessels, including the carotid arteries and cavernous sinuses; vasculitis with thrombosis; hemorrhage and tissue infraction; acute neutrophilic inflammation (Fig 1). Treatment involves aggressive wide surgical debridement, intravenous amphotericin B (1.0 to 1.5 mg/Kg/day with total dose of 2.5 to 4 gram) or lipid preparation of amphotericin B; and possible correction of the underlying immunocompromised status.

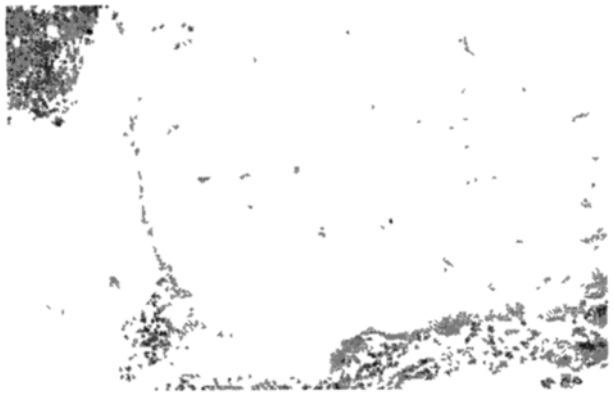

Fig. 1. *Acute necrotizing fungal rhinosinusitis - Showing areas of bland necrosis, acute inflammatory infiltrate and fungal hyphae of zygomycosis; H & E X 33.*

Chronic invasive fungal rhinosinusitis: This condition can be distinguished from other two types of invasive fungal rhinosinusitis by a chronic course, dense accumulation of hyphae, and an association with orbital apex syndrome (extension of fungal infection from ethmoid sinus to the ipsilateral orbit) (Fig 2). A retrospective analysis of 789 consecutive cases of chronic inflammatory sinusitis at Mayo

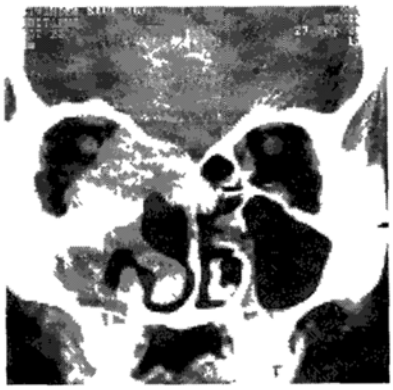

Fig. 2a.

Fig. 2a & 2b. *Chronic invasive fungal rhinosinusitis : CT scan axial and coronal cut showing sino-orbital extension.*

clinic revealed an overall incidence of invasive fungal sinusitis of 0.004%.[25]

Clinically the disease takes a chronic, recurring course and may be seen in patients with diabetes mellitus. The orbital apex syndrome is characterized by decreasing vision and ocular immobility due to a mass in the superior portion of the orbit. The condition may be misdiagnosed as inflammatory pseudotumor. Histopathology shows fungal invasion into the mucosa and occasionally in blood vessels; a chronic inflammatory infiltrate of lymphocytes, giant cells and necrotizing granulomas. The condition may begin as a sinus mycetoma and become invasive. Treatment involves surgical debridement and systemic antifungal drugs. The poor prognosis suggests that it should be treated as aggressively as acute necrotizing (fulminant) rhinosinusitis.

Chronic granulomatous invasive fungal rhinosinusitis: This type, also called indolent fungal sinusitis, is typically found in Sudan, India, Pakistan and United States.[5, 6, 20, 26, 27] Young male villagers are common sufferer of this condition and the type was diagnosed in 14% of patients with chronic sinusitis.[5 6] Patients appear to be immunocompetent and are

infected almost exclusively with Aspergillus flavus.

Clinically the patients present with a syndrome of chronic rhinosinusitis associated with proptosis and occasionally headache. Histopathology reveals mucosa invasive fungi are usually encapsulated within surrounding granulomas with giant cells, and plasma cells (Fig 3). Central microgranulomata of eosinophils, fibrinoid necrosis, fibrosis, and vasculitis have also been noted.[27] Occasional fungal hyphae are seen as halo inside the giant cells (Fig 4).

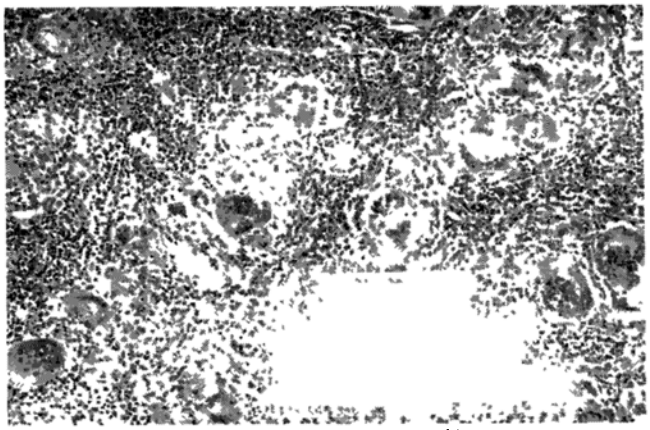

Fig. 3. *Chronic granulomatous invasive fungal rhinosinusitis : Showing granulomatous reaction, H & E X33*

Untreated lesion spreads to orbit, dura and brain. Treatment involves proper surgical removal of the mass. Additionally treatment with Itraconazole at a dose of 5 to 10 mg/Kg/day appears to decrease the high postoperative relapse rate.[28, 29]

Fungal ball (sinus mycetoma): It is characterized by extramucosal accumulation of fungal hyphae within the sinus cavity; usually one sinus (maxillary) is involved. Only rarely they are found in the ethmoid or frontal sinuses. Sinus mycetoma had been reported in 4 to 26% of all chronic inflammatory sinusitis cases undergoing surgery.[5, 25] A. flavus is commonly isolated from patients in India, Sudan and other tropical countries.[5, 6, 26, 27] In contrast, A. fumigatus is the common etiological agent from patients in USA.[20] Dematiaceous hyphomycetes fungi are occasionally reported to cause fungal ball formation.[5, 11] The disease is reported in immunocompetent host.

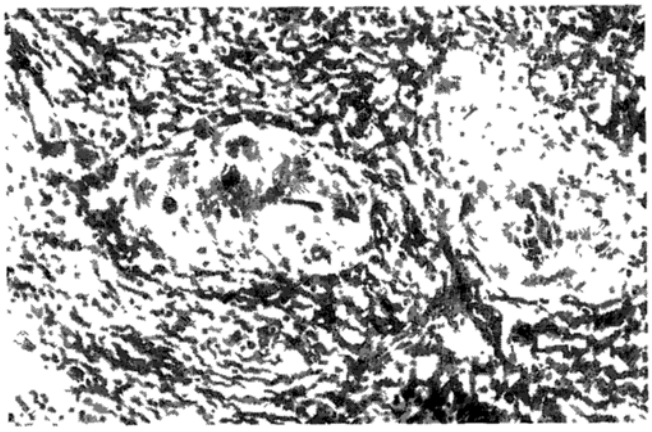

Fig. 4. *Chronic granulomatous invasive fungal rhinosinusitis : Showing fungal hyphae withing the giant cell, Grocott methanamine silver stain X66.*

The patients present with nasal obstruction, chronic sinusitis, facial pain, or a fetid smell (cacosmia). Nasal polyps and bacterial sinusitis may be associated conditions. Histopathology shows dense accumulation of fungal elements in mucoid matrix with low-grade chronic inflammation in adjacent mucosa (Fig 5). Fungi sometimes fail to grow since fungal elements in fungal ball have a low viability.[30] To diagnose sinus mycetoma five criteria are proposed: [31]

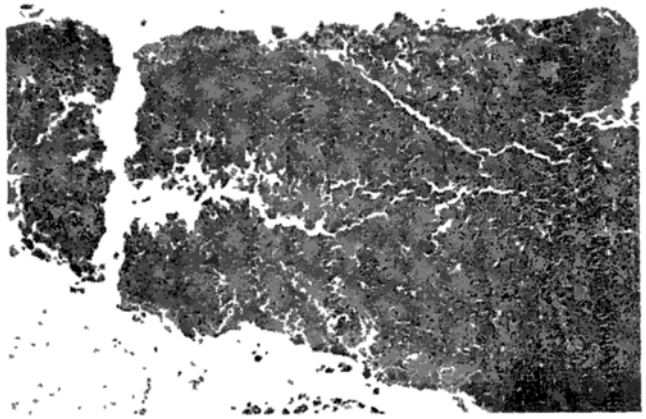

Fig. 5. *Fungal ball (Sinus mycetoma) : Showing fungal ball in the sinuses, PAS X 33.*

Radiologic evidence of sinus opacification with or without associated flocculent calcifications.

2. Mucopurulent, cheesy, or clay like material within a sinus.
3. A matted, dense conglomeration of hyphae separates from but adjacent to sinus respiratory mucosa.
4. A chronic inflammatory response of variable intensity in the mucosa adjacent to fungal elements. The response includes lymphocytes, plasma cells, mast cells, and eosionophils without an eosinophil predominance or granulomatous response. Allergic mucin is absent on haematoxylin-eosin-stained material.
5. No histologic evidence of fungal invasion of mucosa, associated blood vessels, or underlying bone visualized

microscopically on Gromori methanamine silver or other special stains for fungus.

Treatment involves surgical removal of fungal ball along with adequate resection of associated obstructive or significantly diseased sinonasal mucosa. If a significant risk factor like oral-sinus fistula is found, surgical repair may be required to prevent recurrence. Antifungal drugs are not indicated. The importance of detecting precipitating antibody in follow up is highlighted for both sinus mycetoma and chronic invasive fungal sinusitis. Precipitin antibody becomes negative or titer is reduced after surgery and it reappears in patients with recurrence or progression of lesions.[5]

Allergic fungal rhinosinusitis: It is an increasingly recognized type of chronic, recurring hypertrophic sinus disease (HSD). It is a non-tissue invasive fungal process, representing an allergic/hypersensitivity response to the presence of extramucosal fungi within the sinus cavity possibly akin to ABPA. The overall incidence of AFS is estimated at 5-10% of all HSD cases undergoing surgery.[18, 25, 32] The common causes of allergic fungal sinusitis are the dematiaceous hyphomycetes including Curvularia sp., Bipolaris sp., Pseudallescheria boydii, and the hyaline hyphomycetes such as Aspergillus sp. and Fusarium sp.[33, 34]

Clinically the disease should be suspected in patients with atopy and chronic, often intractable, sinusitis and nasal polyposis. Most have pansinusitis and many have multiple sinus operations by the time of diagnosis. Patients often have asthma, allergic rhinitis, eosinophilia, and elevated total and fungus specific IgE concentration. Involved sinuses contain brown or greenish black material with the consistency of peanut butter or cheese. This material has been called

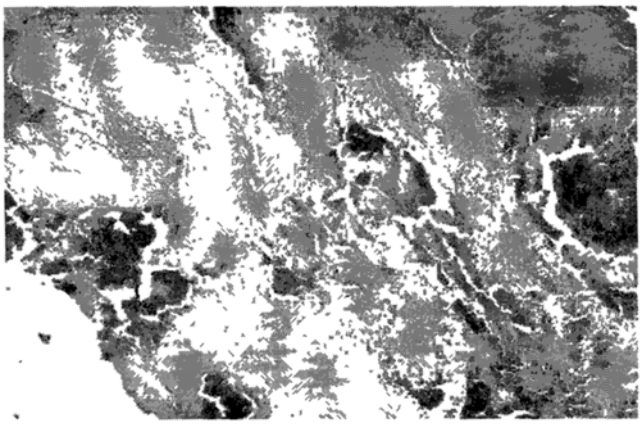

Fig. 6. *Allergic fungal rhinosinusitis : Showing allergic mucin in sinuses, H & E X 13.2.*

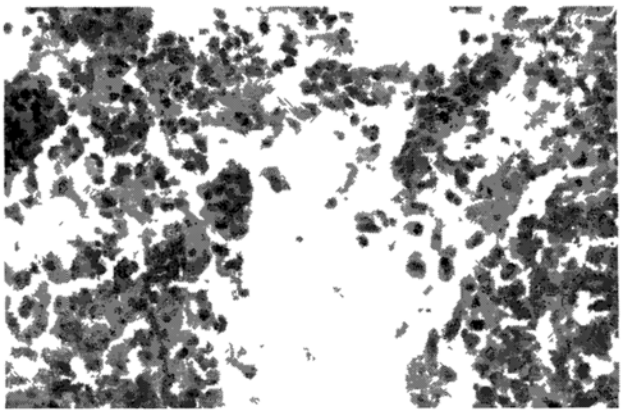

Fig. 7. *Allergic fungal rhinosinusitis : Showing numerous eosinophils with charcoat leyden crystals H & E X 13.2.*

"allergic mucin" and contains laminated accumulation of intact and degenerating eosinophils, charcot-leyden crystals, cellular debris and sparse hyphae (Fig 6 & 7). The diagnostic criteria for allergic fungal sinusitis consist of following features: [20, 35]

1. Radiologically confirmed sinusitis, characteristic computed tomography (CT) signs of serpiginous areas of high attention in affected sinuses.
2. Surgically obtained characteristic allergic mucin
3. Presence of fungal hyphae in allergic mucin or fungal culture is positive in properly collected sinus content in an otherwise characteristic patient
4. No histopathologic evidence of mucosal fungal invasion, mucosal necrosis, granulomata, or giant cells.
5. Other fungal rhinosinusitis disorders must be excluded

In a study for pre-operative diagnosis, it was found that combination of presence of presence of nasal polyp, hyper attenuation in CT scan and specific IgE have a high preoperative diagnostic value.[36] However, those should not be considered in isolation because considerable overlap occurs in other types.

Treatment involves endoscopic removal of polyps and inflammatory material to establish aeration and drainage of involved sinuses as essential first step. Repeated endoscopic surgery obliterates anatomic landmarks and increases the risk of complication and that may necessitate open surgery in some patients.[20] Oral corticosteroid therapy may be indicated for clinical improvement and to prevent recurrence. Patients are given oral corticosteroid post-operatively at 0.5 mg/Kg daily as a single morning dose for 2 weeks, then same dose every other morning for several weeks, with a gradual taper to 7.5 to 5.0 mg every other morning for 3 months postoperatively, then maintained on

5.0 mg every other morning upto one year, or longer in individual cases.[35] Occasionally short-acting intranasal conrticosteroids are prescribed on a long-term basis.[37] Twice daily sinus irrigation with warm isotonic saline with a bulb irrigator or a water pik device with a Grossan Sinus Irrigator tip may prevent impaction of mucous.[20] Allergen immunotherapy possibly help to reduce recidivism.[38] Follow up measurements of total IgE have been shown to reflect the patient's clinical status, falling with disease remission and rising with exacarbation.[35]

IS THE CATEGORIZATION A RESOLVED ISSUE?

The categorization of fungal rhinosinusitis is still controversial and open to discussion. Rowe-Jones and Moore-Gillon (1994) proposed a chronic destructive but non-invasive (semi-invasive) form of rhinosinusitis.[39] It is characterized by sinus expansion and bony erosion, but with no histologic evidence of tissue invasion. In this state, the pathogens results in progressive, chronic inflammation intermediate between allergic, sinus mycetoma and chronic invasive state. Even though inflammation and bone erosion was evident, these cases had not progressed to produce the facial mass or proptosis associated with invasive disease. Such example of semi-invasive pulmonary aspergillosis also exist.[40] However, this entity may be variant of the non-invasive type in which the fungal mass destroys the sinus wall by pressure.[41] In characterizing chronic non-invasive fungal rhinosinusitis, all authors refers to fungal ball or AFS. However, difference between this entity and the fungus ball group is that their clinical course was more violent than fungus ball; they need more extensive endoscopic operation and longer follow-up. The similarity between destructive non-invasive fungal rhinosinusitis and AFS is the long course of disease, the erosive appearance in CT scan (Fig 8), the need for extensive endoscopic surgery and the long follow-up period. The differences between these two groups are the different pathological appearance, immune status and treatment. The treatment protocol of the destructive non-invasive fungal rhinosinusitis is still to be settled.[42]

Fig. 8. *CT scan of PNS coronal cut showing destruction of lamina papyracea.*

In diagnosis of AFS, detection of fungi allergic mucin is important. But because of sparse hyphae occasionally fungal stain is negative. Thus the categorization of this entity has remained controversial especially with the description of two more entities - 'Eosinophilic fungal rhinosinusitis' (EFRS) and 'Eosinophilic mucin rhinosinusitis' (EMRS).[43, 44] This has suggested that the traditional classification list should be changed by including or even substituting the diagnostic category of EFRS for AFS and by adding the entity EMRS. Ponikau et al. described an alternative theory that proposed a different mechanism for AFS and could be applied more universally to encompass chronic rhinosinusitis (CRS) as well.[45] Using a sensitive detection method (nasal lavage) their initial study demonstrated that 93% of patients with CRS had fungi present in tissue specimens. Unlike AFS, however, they did not find type I allergy, elevated total IgE levels, or elevated fungal specific serologies to be prevalent in their study group. Thus, they offered the hypothesis that CRS is in fact cell-mediated response to fungal elements and suggested the new term EFRS. However, they identified fungus in the nasal lavage from 100% of healthy volunteers, demonstrating the ubiquitous nature of these organisms and the sensitivity of their methods and raising the question of pathogenicity of fungi. Lebowitz et al. proposed that using standard laboratory method (specimen were treated with sputolysin like processing of sputum), fungi can be readily identified in the surgical specimens of patients undergoing endoscopic sinus surgery for CRS and analysis of mucus is a reasonable reflection of the overall disease process.[46] Thus the question remains whether a separate, unrecognized form of non-allergic, fungal eosinophilic inflammation exists that can lead to a similar clinical presentation.

Ferguson[43] described EMRS as a distinct entity following up on what Cody et al.[47] had called an allergic fungal sinusitis like syndrome. She proposed a strong argument that in EMRS the driving force is not a fungal hypersensitivity but rather is a systemic deregulation associated with both upper and lower airway eosinophilia[43]. Eosinophilic mucin could be present and cause sinusitis without the presence of fungi. EMRS is always bilateral disease, occurs in older patients in contrast to AFS and asthma in a common association.

Aspirin sensitivity is seen in nearly 50% of patients. Although the significant immunological differences between AFS and EMRS are not well defined, the treatment implications may be minimal because systemic steroids are therapeutically effective in both these conditions.

The confusion regarding the definition of AFS is further intensified with well-documented reports of histologic invasion in cases of AFS.[7 48] Even, Klapper et al.[49] documented foci of granulomatous inflammation in a patient of AFS with orbital apex involvement. Thakar et al.[7] claimed that the lack of similar invasive histopathologic features in other reports of AFS may possibly relate to pathologic sample errors. Thus, it cast doubts on the discrete compartmentalization of fungal sinusitis into invasive and non-invasive, Some workers support the view that different types of fungal sinusitis represent a progressive spectrum of disease with initial colonization to the semi-invasive, allergic or invasive forms.[50 51] Such a progression may be precipitated by a change of host defenses.[52]

Lastly, the distinction of chronic granulomatous invasive type from chronic invasive type is also not beyond controversy. In chronic granulomatous sinusitis, an enlarging mass is seen in the check, orbit, nose and paranasal sinuses. Proptosis is often a prominent feature. Histopathologically, a granulomatous response is seen with considerable fibrosis. Non-caseating granulomata with foreign body or Langerhan's type of giant cells may be seen, sometimes with vasculitis, vascular proliferation and perivascular fibrosis. Hyphae on many occasions are scanty. A. flavus is the primary agent isolated from these cases.[20 27 35] In contrast, chronic invasive type is characterized as dense accumulation of hyphae, presence of vascular invasion, sparse inflammatory reaction, A. fumigatus isolation and association with orbital apex syndrome, diabetes mellitus, and corticosteroid treatment.[20 25] However, such distinction is not recognized by other workers.[11 53 54] Indeed, clinico-pathological distinctions between these two types are not sharp. Both have a chronic course and predominant orbital involvement. Isolation of different type of Aspergillus species may represent separate geographical distribution and different tissue responses may depend on host immune status.

CONCLUSIONS

While the controversy of categorization is unsettled, the following decisions are important to clinicians. All cases of chronic rhinosinusitis not responding to standard therapy should be investigated for fungal rhinosinusitis. The most important issue in treating a case of fungal rhinosinusitis is to determine whether the disease is invasive or non-invasive. The acute fulminant type should be treated with aggressive surgery and amphotericin B therapy. Chronic invasive disease needs antifungal therapy besides surgical removal. The non-invasive types i.e. fungal ball and AFS are cured by surgery alone and may not require antifungal therapy, although recurrence is possible.

REFERENCES

1 Holt GR, Standefer JA, Brown WE. Gates Ga Infectious diseases of the sphenoid sinus Laryngoscope 1984, 94 330-335

2 Stammberger H, Jakse R, Beanfort F Aspergillosis of paranasal sinuses Ann Otol Rhinol Laryngol 1984, 93 251-256

3 Hora JF Primary aspergillosis of the paranasal sinuses and associated areas Laryngoscope 1965, 75· 768-773

4 Grewal RS, Khurana S, Aujla KS, Goyal SC Incidence of fungal infections in chronic maxillary sinusitis Indian J Pathol Microbiol 1990, 33. 339-343

5 Chakrabarti A. Sharma SC, Chander J Epidemiology and pathogenesis of paranasal sinus mycoses Otolaryngol Head Neck Surg 1992, 107: 745-750

6 Panda NK, Sharma SC, Chakrabarti A, Mann SBS Paranasal sinus mycoses in north India. Mycoses 1998, 41: 281-286

7 Thakar A, Sarkar C, Dhiwakar M, Bahadur S, Dahiya S Allergic fungal sinusitis expanding the clinicopathologic spectrum Otolaryngol head Neck Surg 2004, 130 209-216

8 Murthy JM, Sundaram C, Prasad VS, Purohit AK, Rammurti S, Laxmi V Sinocranial aspergillosis. a form of central nervous system aspergillosis in south India Mycoses 2001, 44 141-145

9 Rupa V, Jacob M, Mathews MS, Job A, Kurien M, Chandi SM Clinicopathological and mycological spectrum of allergic fungal sinusitis in south India Mycoses 2002, 45 364-367

10 Rane S, Jayaraman A, Holla VV Allergic fungal sinusitis – a case report Indian J Pathol Microbiol 2003, 46 450-451

11 Washburn RG, Kennedy DW, Begley MG, Henderson DK, Bennett JE Chronic fungal sinusitis in apparently normal hosts Medicine 1988, 67 231-247

12 Plaignaud M Observation sur un fungus du sinus maxillaire J Chir (Paris) 1791, 1 111-116

13 Schubert P. Zur Casuistik der. Aspergillus mycosen Dtsch Arch Klin Med 1885, 36. 162-179

14 Oppe W Zur Kentniss der schimmelmykosen beiden Menschen Zbl Allg Path 1987, 8· 301-306

15 Hora JF Primary aspergillosis of the paranasal sinuses and associated areas Laryngoscope 1965, 75 768-773

16 McGill TJ. Simpson G, Healey GB Fulminant aspergillosis of the nose and paranasal sinuses a new clinical entity Laryngoscope 1980, 90 748-754.

17 Miller JW, Johnston A, Lamb D Allergic aspergillosis of the maxillary sinuses Thorax 1981, 36 710
18 Katzenstein AA, Sale SR, Greenberger PA Allergic Aspergillus sinusitis A newly recognized form of sinusitis J Allergy Clin Immunol 1983, 72 82-93
19 Allphin AL, Strauss M, Abdul-Karim FW Allergic fungal sinusitis problems in diagnosis and treatment Laryngoscope 1991, 101 815-820
20 deShazo RD, Chapin K, Swain RE Fungal sinusitis New Eng J Med 1997 337 254-259
21 Radner AB, Witt MD, Edwards JWE Jr Acute invasive rhinocerebral zygomycosis in an otherwise healthy patient case report and review Clin Infect Dis 1995 20 163-166
22 Blitzer A, Lawson W fungal infections of the nose & paranasal sinuses Otolaryngol Clin North Am 1993, 26 1007-1035
23 Talbot GH, Huang A, Provencher M Invasive Aspergillus rhinosinusitis in patients with acute leukaemia Rev Infect Dis 1991, 13 219-232
24 Scharf JL, Soliman AMS Chronic Rhizopus invasive fungal rhinosinusitis in an immunocompetent host Laryngoscope 2004 114 1533-1535
25 Ferierio JA, Carlson BA, Cody DT Paranasal sinus fungal balls Head Neck 1997, 19 481-486
26 Milosev B, Mahgoub ES, Abdell AO, Hassan O, Mel A Primary aspergillosis of paranasal sinuses in Sudan – a review of 17 cases Br J Surg 1969, 56 132-137
27 Veress B, Malik OA, el-Tayeb AA, el-Daoud S Mahgoub ES, el-Hassan AM Further observations on primary paranasal Aspergillus granuloma in the Sudan a morphological study of 46 cases Am J Trop Med Hyg 1973, 2 765-772
28 Gumaa SA, Mahgoub ES, Hay RJ Post-operative responses of paranasal Aspergillus granuloma to itraconazole Trans R Soc Trop Med Hyg 1992, 86 93-94
29 Panda NK, Balaji P, Chakrabarti A, Sharma SC, Reddy CEE Paranasal sinus aspergillosis its categorization to develop a treatment protocol Mycoses 2004, 47 277-283
30 Campbell MJ, Clayton YM Bronchopulmonary aspergillosis a correlation of the clinical and laboratory findings in 272 patients investigated from bronchopulmonary aspergillosis Am Rev Resp Dis 1964, 89 189-196
31 deShazo RD, O'Brien M, Chapin K, et al Criteria for diagnosis of sinus mycetoma J Allergy Clin Immunol 1997, 99 475-485
32 Collins MM Nair SB, Wormald PJ Prevalence of non-invasive fungal sinusitis in south Australia Am J Rhinol 2003, 17 127-132
33 Chhabra A, Handa KK, Chakrabarti A, Mann SBS, Panda N Allergic fungal sinusitis clinicopathological characteristics Mycoses 1996, 39 437-441
34 Chakrabarti A, Sharma SC, Panda N, Das A Paranasal sinus mycoses Advances Med Mycol 1997, 2 39-59
35 Schubert MS Allergic fugal sinusitis Otolaryngol Clin N Am 2004, 37 301-326
36 Diwakar M, Thakar A, Bahadur S, et al Preoperative diagnosis of allergic fungal sinusitis Laryngoscope 2003, 113 688 694
37 Corey JP, Delsupehe KG, Ferguson BJ Allergic fungal sinusitis allergic infectious or both? Otolaryngol Head Neck Surg 1995, 113 110-119
38 Marple BF Allergic fungal rhinosinusitis current theories and management strategies Laryngoscope 2001, 111 1006-1019
39 Rowe-Jones JM, Moore-Gillon V Destructive non-invasive paranasal sinus aspergillosis component of a spectrum of disease J Otolaryngol 1994, 23 92-96
40 Gefter WB, Weingard TR, Epstein DM et al "Semi-invasive" pulmonary aspergillosis Radiology 1981, 140 313-321
41 Robb PJ Aspergillosis of the paranasal sinuses a case report and historical perspective J Laryngol Otol 1986, 100 1071-1077
42 Uri N Cohen-Kerem R, Elmalah J, Doweck J, Greenberg E Classification of fungal sinusitis in immunocompetent patients Otolaryngol Head Neck Surg 2003, 129 372-378
43 Ferguson BJ Eosinophilic mucin rhinosinusitis a distinct clinicopathological entity Laryngoscope 200, 110 799-813
44 Thrasher RD, Kingdom TT Fungal infections of the head and neck an update Otolaryngol Clin N Am 2003, 36 577-594
45 Ponikau JU Sherris DA Kern EB The diagnosis and incidence of allergic fungal sinusitis Mayo Clin Proc 1999 74 877-884
46 Lebowitz RA, Waltzman MN, Jacobs JB, Pearlman A Tierno PM Isolation of fungi by standard laboratory methods in patients with chronic rhinosinusitis Laryngoscope 2002, 112 2189-2191
47 Cody DT, Neel HS Ferreiro JA Allergic fungal sinusitis the Mayo clinic experience Laryngoscope 1994, 104 1074-1079
48 Schubert MS, Goetz DW Evaluation and treatment of allergic fungal sinusitis, I Demographics and diagnosis J Allergy Clin Immunol 1998, 102 387-394
49 Klapper SR, Lee AG, Patrinely JR, et al Orbital involvement in allergic fungal sinusitis Ophthalmology 1997, 104 2094-2100
50 Sarti JE Lucente FE Aspergillosis of the paranasal sinuses Ear Nose Throat J 1988, 67 824-831
51 Rowe Jones J Paranasal aspergillosis a spectrum of disease (editorial) J Laryngol Otol 1993, 107 773-774
52 Gungor A, Adusumilli V, Corey JP Fungal sinusitis progression of disease in immunosuppression – a case report Ear Nose Throat J 1998, 77 207 215
53 Milroy CM, Blanshard JD, Lucas S Michaels L Aspergillosis of the nose and paranasal sinuses J Clin Pathol 1989, 42 123-127
54 Granville L, Chirala M, Cernoch P Ostrowski M Thuong LD Fungal sinusitis Histologic spectrum and correlation with culture Hum Pathol 2004, 35 474-481

Address for Correspondence:
Dr. Arunaloke Chakrabarti
Department of Medical Microbiology
PGIMER, Chandigarh
Chandigarh-160012
e-mail chakrab@sancharnet in
Phone· +91 172 2747585 extn 5156/5172
Fax· +91 172 2744401/2745078